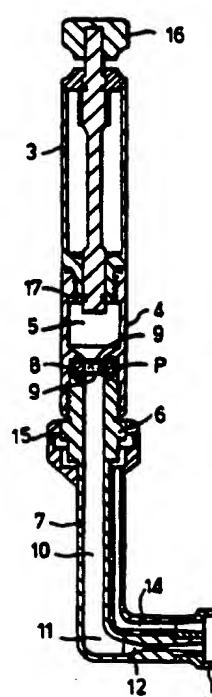
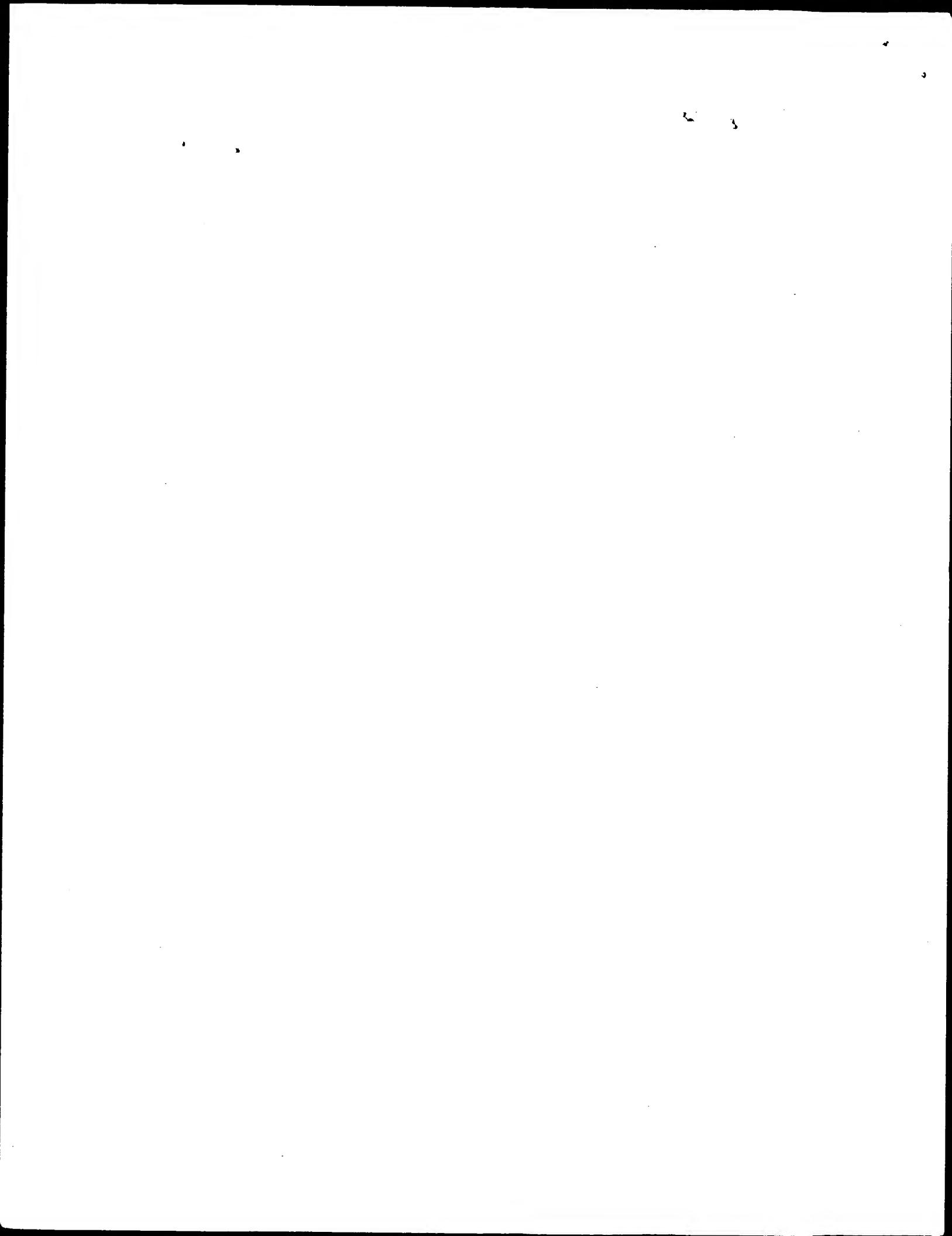


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

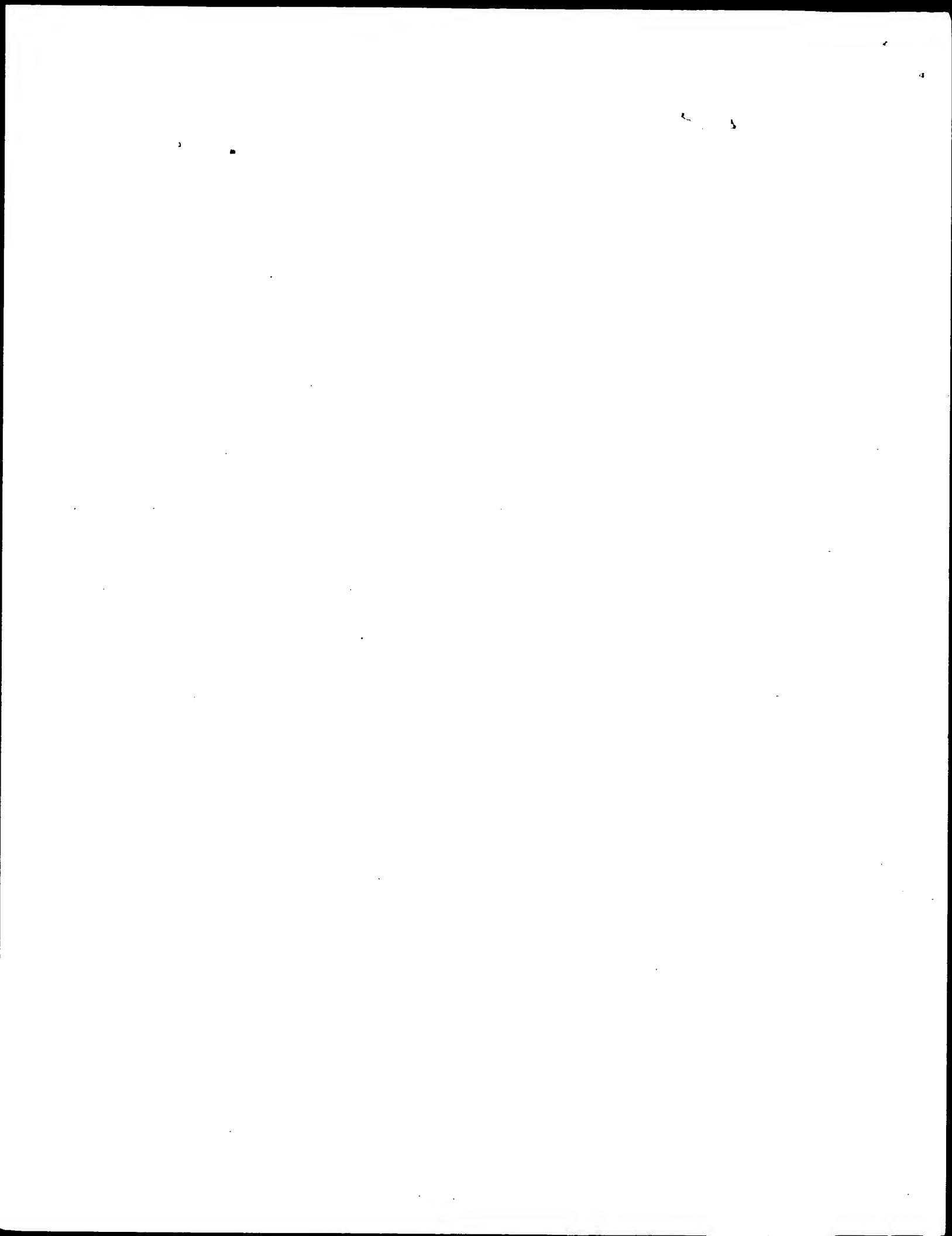
(51) International Patent Classification ⁶ : A61M 5/307		(11) International Publication Number: WO 96/25190 (43) International Publication Date: 22 August 1996 (22.08.96)
<p>(21) International Application Number: PCT/GB96/00340</p> <p>(22) International Filing Date: 14 February 1996 (14.02.96)</p> <p>(30) Priority Data: 9502879.1 14 February 1995 (14.02.95) GB PCT/GB95/03016 21 December 1995 (21.12.95) WO </p> <p>(34) Countries for which the regional or international application was filed: AL et al.</p> <p>(71) Applicant (for all designated States except US): OXFORD BIOSCIENCES LIMITED [GB/GB]; The Magdalen Centre, The Oxford Science Park, Oxford OX4 4GA (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BELLHOUSE, Brian, John [GB/GB]; The Lodge, North Street, Islip, Oxfordshire OX5 2SQ (GB). BELL, John [GB/GB]; The Dairy, Lower Street, Islip, Oxfordshire OX5 5SG (GB). GREENFORD, John, Christopher [GB/GB]; 11 Park Crescent, Abingdon, Oxfordshire OX14 1DF (GB). SARPHIE, David, Francis [US/GB]; 78 Hailey Road, Witney, Oxfordshire OX8 5SH (GB).</p> <p>(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).</p>		
<p>(54) Title: TRANS-MUCOSAL PARTICLE DELIVERY</p> <p>(57) Abstract</p> <p>A needleless syringe comprising an elongate tubular nozzle (7) having a bend (11) part way along its length, a source (8, 21) of particles (P) of a therapeutic agent, and energising means (3) for producing in the nozzle (7) a supersonic condition to cause the particles (P) to be propelled from the nozzle (7) for trans-mucosal delivery of local or systemically-active therapeutic compounds.</p> 		



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	America	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BP	Bolivia Poco	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Burkina	JP	Japan	PT	Portugal
BR	Brazil	KR	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central Africas Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	L1	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
ES	Ecuador	MG	Madagascar	UA	Ukraine
FI	Finland	ML	Mali	UG	Uganda
FR	France	MN	Mongolia	US	United States of America
GA	Gabon	MQ	Mauritania	UZ	Uzbekistan
				VN	Viet Nam



TRANS-MUCOSAL PARTICLE DELIVERY

In our earlier WO94/24263, we disclose a non-invasive drug delivery system involving the use of a needleless 5 syringe which fires particles of a therapeutic agent in controlled doses into body tissue, e.g. through the intact skin, or delivers genetic material into living cells. The syringe described in the earlier application is constructed as an elongate tubular nozzle, a rupturable membrane 10 initially closing the passage through the nozzle adjacent to the upstream end of the nozzle, particles of a therapeutic agent located adjacent to the membrane, and energising means for applying to the upstream side of the membrane a gaseous pressure sufficient to burst the 15 membrane and produce through the nozzle a supersonic gas flow in which the particles are entrained.

As explained in the earlier specification, the particles of the therapeutic agent may be powdered drugs for all kinds of therapeutic use. Similarly the earlier 20 specification explains the parameters of particle size (preferably 10-40 μm) density (preferably 0.5-2.0 g/cm^3), and velocity (preferably 200-2500 m/sec), and momentum density, that is particle momentum divided by particle frontal area, (preferably 4-7 $\text{kg}/\text{sec}/\text{m}$), which have been 25 found to be appropriate for adequate target penetration. These parameters are unchanged but we have now devised a modification of the particle delivery system.

Syringes of the above type for transdermal delivery of drugs have generally had an elongate shape with a straight 30 nozzle portion terminating in an outlet directed in the axial direction of the nozzle. This is perfectly satisfactory for drug delivery to most external parts of the body. However, this is not universally so. For example, for many dental operations the appropriate sites 35 for delivery of a local anaesthetic such as lignocaine are into the gums or palate close to the teeth. These injections can be very painful and can cause distress both

to the dentist and the patient. It would therefore be very desirable to be able to use the new needleless injection system for injections into the palate and other relatively inaccessible sites within the mouth including the cheeks 5 and gums. However it is difficult to position the tip of the previously proposed needleless syringes in the appropriate positions with the axis of the nozzle substantially perpendicular to the mucosal surface.

According to the present invention, a needleless 10 syringe comprises an elongate tubular nozzle, which has a bend a part way along its length, and an upstream end of which is, or is arranged to be, connected to a source of gaseous pressure; means for suddenly releasing the gas to create a supersonic condition within the nozzle; and a 15 source of particles of a powdered therapeutic agent which are arranged to be propelled from the downstream end of the nozzle upon the gas release.

The invention also includes a method of delivering a therapeutic agent to an internal mucosal surface such as 20 the gums, cheeks or palate of the mouth, the vagina, the rectum or the nasal or ocular mucosa, the method comprising applying the new syringe using the bend in the nozzle to enable the downstream end of the nozzle to be directed substantially normally to the mucosal surface, and 25 operating the syringe to cause the particles of powdered therapeutic agent to be propelled into the mucosal surface.

It is thus possible to deliver therapeutic agents into the palate, cheeks, gums and other mucosal tissue, for local and systemic applications using the new needleless 30 injection system.

Examples of therapeutic agents which may be delivered in this way include topically active local anaesthetics, such as lignocaine hydrochloride, lignocaine base, 35 ropivacaine hydrochloride, bupivacaine, procaine, prilocaine, tetracaine, etidocaine, benzocaine, cocaine and similar, which may be mixed with epinephrine (adrenaline) to cause vasoconstriction and prolong the anaesthetic

effect. Alternatively, the therapeutic agent may be a systemically-active organic or inorganic small molecule, peptide, natural or recombinant protein, vaccine or oligonucleotide such as insulin, growth hormone, glucagon, 5 atropine, alprazolam, calcitonin, desmopressin, 5HT, dihydroergotamine, interleukin, metal ions and similar.

The nozzle may be flexible, for example comprising a metal coil, which may be embedded within a pliable material, such that the bend may be adjusted to a desired 10 angle, and is then stable in the adjusted position. This will facilitate application of the downstream end of the nozzle to various inaccessible parts of the patient's mouth or other mucosal cavities.

The release means may comprise a rupturable membrane 15 which initially closes the passageway through the nozzle; and a valve for releasing gas from the source into a chamber behind the membrane until the membrane ruptures. Alternatively, the release means may be a fast self opening valve having a closure element which is initially held in 20 a closed position, and means for releasing the element whereupon the element moves to an open position under the pressure of the gas source.

The supersonic condition may be a supersonic gas flow 25 in which the particles are entrained, as described more fully in WO 94/24263. However, if the supersonic flow is created upstream of the bend it has been found that the flow may have difficulty in passing around the bend without suffering unacceptable deceleration. To counteract this, it is proposed that the part of the nozzle downstream of 30 the bend is narrower than the part upstream of the bend so that the gas flow is accelerated to supersonic speed only after the gas has travelled around the bend.

Surprisingly, we have found that with this construction the gas can pass through the wider upstream 35 portion of the bend at moderate speed, before being rapidly accelerated to a necessary supersonic speed at the narrower portion downstream of the bend. The narrower portion is

preferably of convergent/cylindrical or convergent/divergent shape with the convergent portion being of greater conicity than the cylindrical or divergent portion. The means for initiating the gas flow can be positioned as remotely as is convenient from the nozzle outlet, e.g. away from the patient's mouth. The particles of therapeutic agent may be entrained in the gas flow in the upstream portion of the nozzle and accelerated to supersonic speed as they pass through and out of the downstream portion of the nozzle.

The particles to be entrained may be initially located between two rupturable diaphragms extending across the interior of the nozzle; and if the supersonic flow is initiated by a rupture of a membrane, the rupturable membrane may be provided by one of the diaphragms.

Instead of the particles being entrained within a supersonic gas flow, the arrangement may be such that the downstream end of the nozzle is provided with a bistable diaphragm, which is movable between an inverted position in which it presents outwardly of the nozzle a concavity containing the particles, and an everted, outwardly convex, position, the arrangement being such that a supersonic shockwave, providing the supersonic condition in the nozzle, is arranged to snap the diaphragm over from its inverted to its everted position, and to catapult the particles outwardly, similarly to the technique described in our earlier international patent application No. PCT/GB 95/03016. The advantages of this system, as compared to the particle-entraining supersonic flow system are its quietness, and the fact that, in dental applications, no gas is ejected from the nozzle into the patient's mouth.

Experiments show that the necessary shockwave to evert the diaphragm can be generated upstream of the nozzle bend and have enough energy to round the bend. This enables the shockwave to be generated remote from the patient's mouth and enables the downstream end of the nozzle, which enters the mouth, to be of small size.

The particles in the concavity of the bistable diaphragm may be covered by a thin barrier film which ruptures upon eversion of the diaphragm. The process of releasing the particles without shedding fragments of the barrier film can be aided by scoring, punching, cutting, or providing other lines of weakness in the barrier film. The film may provide the sole means of retaining the particles in the concavity, or it may be provided to maintain sterility, the particles being otherwise immobilised on the diaphragm.

There are a number of ways in which the particles may be initially retained on the everting diaphragm. First, the particles may be retained by a weak adhesive or cohesive agent, which temporarily binds the particles to the concave face of the diaphragm, and possibly also to one another. The eversion process breaks up the weak particle-diaphragm and weak particle-particle bonds. Examples of appropriate adhesive/cohesive agents are water, ethanol, methanol, glycerol, KY jelly, sucrose solution, trehalose solution and albumin solution, and volatile granulation solvents, such as perfluoro alkanes, which are well known in the tabletting art.

Secondly, the particles could be retained on the diaphragm by freezing. The freezing process can be slow, eg using a standard refrigerator, or rapid, using eg liquid nitrogen or dry ice. If the particles are hygroscopic, then the freezing process harnesses the moisture content in order to bond the particles to the diaphragm, and possibly also to each other. If the particles are thawed after freezing, then the adhesion/cohesion can be maintained.

Thirdly, the particles and diaphragm assembly could be placed in a centrifuge so that the centrifugal acceleration forces the particles onto the concave face of the diaphragm. This compaction process "sticks" the particles to the diaphragm and produces an even distribution of particles.

These methods of retaining the particles on the diaphragm form independent aspects of the invention and are applicable to all applications of the evertng diaphragm technology, as described in earlier PCT/GB 95/03016, and 5 not only when applied to a nozzle having a bend between upstream and downstream portions.

Irrespective of how the supersonic flow or shockwave is produced, in both cases the velocity is increased if the gas which is released into the nozzle is lighter than air, 10 eg helium. The velocity is also increased if the nozzle is initially filled with a gas which is lighter than air, eg helium.

Examples of syringes constructed in accordance with the present invention are illustrated in the accompanying 15 drawings, in which:

Figures 1 to 4 are axial sections of four examples of syringe; and,

Figures 5 and 6 show an evertable diaphragm of the second, third and fourth examples before and after firing, 20 respectively.

The syringe illustrated in Figure 1 has a cylindrical reservoir 3 initially containing helium under a pressure of between 40 and 100, eg about 80, bar. The reservoir, which can be provided as a separate item, is sealed and screwed 25 to a body 4 containing a rupture chamber 5. The body 4 is in turn screwed to a head 6 of a nozzle 7. Sandwiched and sealed between a flange on the body 4 and the end of the head 6 is a sealed capsule 8 consisting of a pair of rupturable membranes 9, spaced at their edges by a ring and 30 containing between them powder particles P of a therapeutic agent, such as lignocaine alone or in an inert carrier. Instead of screw connections, other attachment means, such as bayonet couplings or snap fits may be used.

The nozzle 7 is of right angular shape and 35 incorporates an upper longer, wider passageway 10 upstream of a bend 11, and a shorter narrower convergent/divergent portion 12 projecting laterally from the upstream portion

downstream of the bend 11. The nozzle terminates in a soft annular spacer 13 from within which an exhaust passage 14 leads back along the nozzle 7 to exhaust ports 15 in the head 6.

5 In use helium from the reservoir 3 is released into the rupture chamber 4 upon depression of a plunger 16 and consequential opening of a valve 17. When the pressure in the chamber 5 has built up sufficiently, the membranes 9 are ruptured, releasing a flow of gas through the nozzle 7
10 with the particles entrained in the flow. The flow passes around the bend 11 and into the narrower portion 12, which has a shorter convergent entry part followed by a short cylindrical part leading to a larger divergent part of lesser angle of conicity than the convergent part. In
15 doing so the gas flow is accelerated to supersonic speed of Mach 2 to Mach 8 and the particles are carried by the gas out through the spacer 13, which has previously been placed in contact with the skin, and into the skin. The gaseous shockwave, which is reflected from the skin, passes back
20 through the exhaust passage 14 where its energy is dissipated with minimum noise.

In the Figure 2 example, release of gas into the chamber 5 from the reservoir 3 enables the gas to flow through the passageway 10 in the nozzle so that pressure builds up behind a rupturable membrane 18 in a downstream portion 19 of the nozzle, which projects laterally at 90° to the axis of the upstream portion of the nozzle. The portion 19 contains an evertible bistable diaphragm 20 which is shaped in the form of a dome from a stiff and strong, but resilient, material such as Mylar by thermoforming in suitable jig. The diaphragm has a peripheral flange 21. The concavity of the diaphragm initially contained particles P of a therapeutic agent, which are retained to the diaphragm by one of the methods referred to above. A thin barrier film 22 has its edges sealed to the diaphragm. The downstream portion of the syringe is assembled by inserting the membrane 18 into a
25
30
35

counterbore in the portion 19, until its edges engage an annular shoulder at the end of the counterbore, inserting a spacer sleeve 23 so that it abuts the edge of the diaphragm, inserting the diaphragm as shown in Figure 5, so
5 that its flange 21 engages the end of the spacer, and securing the three parts in place by screwing into the extreme downstream end of the portion 19 a gland nut 24.

In operation, when the gaseous pressure released from the reservoir 3 is sufficient, the membrane 18 ruptures,
10 releasing a shockwave which travels faster than the speed of sound (typically two or three times faster) and which causes the diaphragm 20 suddenly to evert from a downstream concave shape to a downstream convex shape. This causes the barrier film 22 to open and the particles P to be
15 propelled, as shown in Figure 6, at supersonic velocity from the end of the nozzle, in use into the patient's tissue against which the end of the nozzle has previously been placed.

The Figure 3 example differs from the Figure 2 example
20 in that the downstream portion of the nozzle is connected with the upstream portion through a smoothly and curved bend, rather than through an angular bend. Also, the diaphragm 18 is now positioned at the upstream end of the upstream portion of the nozzle, at the outlet of the
25 rupture chamber 5, instead of in the downstream portion. The flange of the evertible diaphragm is directly in engagement with the shoulder at the end of the counterbore in the downstream portion of the nozzle and is held in position by a sealing ring and a gland nut 25. This example operates in the same way as that of Figure 2 except
30 that in this case the supersonic shockwave is produced at the upstream end of the nozzle, upon rupture of the membrane 18, and travels along the upstream and downstream portions of the nozzle before causing eversion of the diaphragm 20 and expulsion of the particles P.
35

The Figure 4 example differs from the Figure 3 example in that there is no rupturable membrane 18. Instead of the

valve 17, operated by the plunger 16, the valve stem 26, which carries the valve closure element 17 at its lower end, is connected to the element by a frusto conical portion 27. As there is no equivalent enlargement at the 5 other end of the stem 26, the pressure in the reservoir 3, acting on the portion 27 continually urges the stem 26 downwardly, and hence the element 17 towards its open position. This is initially prevented by a trigger 28, which is pivoted to a head 29 of the reservoir and urged by 10 a leaf spring 30 to rotate in an anti-clockwise direction as seen in Figure 4, so that a tip 31 of the trigger engages an annular groove 32 in the upper part of the stem. When the trigger is depressed, pivoting clockwise as seen 15 in Figure 4, the tip 31 moves out of the groove 32, allowing the stem 26 to move suddenly downwardly under the high pressure in the reservoir 3, releasing the gas from the reservoir into the nozzle 10, and thus producing a supersonic shockwave which travels along the nozzle and everts the diaphragm 20. The downward movement of the stem 20 26 is limited by engagement of a flange 33, at the upper end of the stem, with the arms of a U-shaped yoke 34, which is insertable through a lateral bore in the head 29, the bore being closed by a screw threaded plug 35.

Although not shown, the nozzle in each case may be 25 prefilled with a gas, such as helium, which is lighter than air. In the Figure 1 example, this case may be contained by a peelable or burstable closure foil at the downstream end of the nozzle.

CLAIMS

1. A needleless syringe comprising an elongate tubular nozzle, which has a bend a part way along its length, and
5 an upstream end of which is, or is arranged to be, connected to a source of gaseous pressure; means for suddenly releasing the gas to create a supersonic condition within the nozzle; and a source of particles of a powdered therapeutic agent which are arranged to be propelled from
10 the downstream end of the nozzle upon the gas release.
2. A syringe according to claim 1, wherein the release means comprises a rupturable membrane which initially closes the passageway through the nozzle; and a valve for
15 releasing gas from the source into a chamber behind the membrane until the membrane ruptures.
3. A syringe according to claim 1, wherein the release means is a fast self opening valve having a closure element
20 which is initially held in a closed position, and means for releasing the element whereupon the element moves to an open position under the pressure of the gas source.
4. A syringe according to any one of the preceding
25 claims, in which the supersonic condition is a supersonic gas flow in which the particles are entrained.
5. A syringe according to claim 4, wherein the part of
30 the nozzle downstream of the bend is narrower than the part upstream of the bend so that the gas flow is accelerated to supersonic speed only after the gas has travelled around the bend.
6. A syringe according to claim 5, wherein the narrower
35 part of the nozzle downstream of the bend has a convergent/divergent or convergent/cylindrical shape.

7. A syringe according to any one of claims 4 to 6, wherein the particles are initially located between two rupturable diaphragms extending across the interior of the nozzle.

5

8. A syringe according to any one of claims 4 to 7, when dependent upon claim 2, wherein the rupturable membrane is provided by one of the diaphragms.

10 9. A syringe according to any one of claims 1 to 3, wherein the downstream end of the nozzle is provided with a bistable diaphragm, which is movable between an inverted position in which it presents outwardly of the nozzle a concavity containing the particles, and an everted, 15 outwardly convex, position, the arrangement being such that a supersonic shockwave, providing the supersonic condition in the nozzle, is arranged to snap the diaphragm over from its inverted to its everted position, and to catapult the particles outwardly.

20

10. A syringe according to claim 9, wherein the particles in the concavity are covered by a thin barrier film which ruptures upon eversion of the diaphragm.

25 11. A syringe according to claim 9 or claim 10, wherein the particles are initially retained on the everting diaphragm by a weak adhesive or cohesive agent.

30 12. A syringe according to claim 9 or claim 10 wherein the particles are initially retained on the everting diaphragm by freezing or centrifuging.

35 13. A syringe according to any one of the preceding claims, incorporating, upstream of the nozzle, a reservoir containing the gas source at a pressure of between 40 and 100 bar.

14. A syringe according to any one of the preceding claims, in which the pressurised gas is a gas which is lighter than air.
- 5 15. A syringe according to claim 14, wherein the gas is helium.
- 10 16. A syringe according to any one of the preceding claims, wherein the nozzle initially contains a gas which is lighter than air.
17. A syringe according to claim 16, wherein the gas within the nozzle is helium.
- 15 18. A syringe according to any one of the preceding claims, wherein the nozzle is flexible so that the bend may be adjusted to a desired angle, and is then stable in the adjusted position.
- 20 19. A syringe according to any one of the preceding claims, wherein the therapeutic agent is a topically active local anaesthetic.
- 25 20. A syringe according to claim 19, wherein the local anaesthetic is lignocaine hydrochloride, lignocaine base, ropivacaine hydrochloride, bupivacaine, procaine, prilocaine, tetracaine, etidocaine, benzocaine, or cocaine.
- 30 21. A syringe according to claim 19 or claim 20, wherein the local anaesthetic is mixed with epinephrine (adrenaline) to cause vasoconstriction and prolong the anaesthetic effect.
- 35 22. A syringe according to any one of claims 1 to 18, wherein the therapeutic agent is a systemically-active organic or inorganic small molecule, peptide, natural or recombinant protein, vaccine or oligonucleotide such as

insulin, growth hormone, glucagon, atropine, alprazolam, calcitonin, desmopressin, 5HT, dihydroergotamine, interleukin, or metal ions.

- 5 23. A syringe according to any one of the preceding claims, wherein the particles have a size of between 10 and 40 μm .
- 10 24. A syringe according to any one of the preceding claims, wherein the particles have a density of between 0.5 and 2.0 g/cm^3 .
- 15 25. A syringe according to any one of the preceding claims, in which the particles are propelled from the downstream end of the nozzle at a velocity of between 200 and 2500 m/sec .
- 20 26. A syringe according to any one of the preceding claims, wherein the momentum density of the particles propelled from the downstream end of the nozzle is between 4 and 7 $\text{kg}/\text{sec}/\text{m}$.
- 25 27. A method of delivering a therapeutic agent to a mucosal surface such as the gums, cheeks or palate of the mouth, the vagina, rectum or nasal or ocular mucosa, the method comprising applying a syringe according to any one of the preceding claims, using the bend in the nozzle to enable the downstream end of the nozzle to be directed substantially normally to the mucosal surface, and operating the syringe to cause the particles of powdered therapeutic agent to be propelled into the mucosal surface.
- 30 28. A method of therapeutic treatment, comprising the trans-mucosal delivery of a particulate agent that provides said therapeutic treatment, which comprises administering the particles to the locus of trans-mucosal administration.
- 35

29. A method according to claim 28, in which the agent has no, or a minor amount by volume of, inert carrier or diluent.
- 5 30. A method according to claim 28 or claim 29, wherein the particles are administered at a velocity in the range between 500 and 1,500, preferably between 750 and 1,000 m/sec; and/or the particles have a size in the range of between 1 and 50, preferably between 10 and 20 μm ; and/or
10 the density of the particles is in the range of between 0.5 and 2.0, preferably substantially 1.0 g/cm³.
- 15 31. A method according to any one of claims 28 to 30, in which the therapeutic agent is a topically active local anaesthetic.
- 20 32. A syringe according to claim 31, wherein the local anaesthetic is lignocaine hydrochloride, lignocaine base, ropivacaine hydrochloride, bupivacaine, procaine, prilocaine, tetracaine, etidocaine, benzocaine, or cocaine.
- 25 33. A syringe according to claim 31 or claim 32, wherein the local anaesthetic is mixed with epinephrine (adrenaline) to cause vasoconstriction and prolong the anaesthetic effect.
- 30 34. A syringe according to any one of claims 28 to 30, wherein the therapeutic agent is a systemically-active organic or inorganic small molecule, peptide, natural or recombinant protein, vaccine or oligonucleotide such as insulin, growth hormone, glucagon, atropine, alprazolam, calcitonin, desmopressin, 5HT, dihydroergotamine, interleukin, or metal ions.

Fig.2.

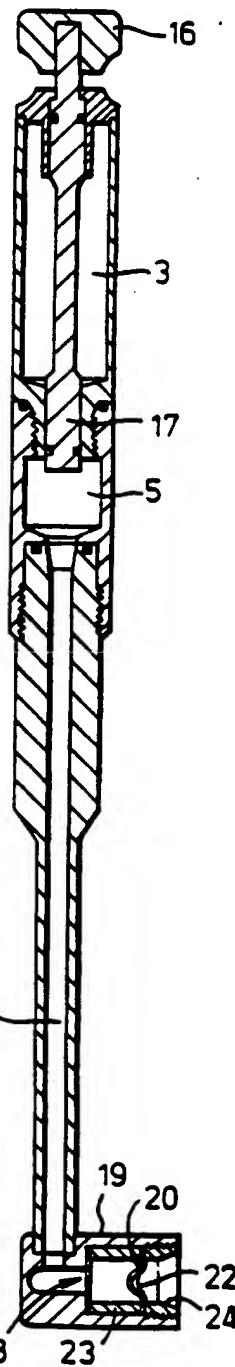
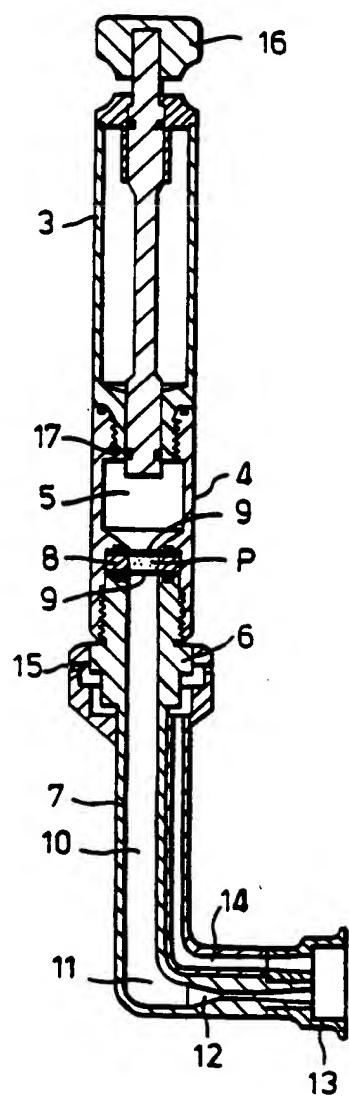
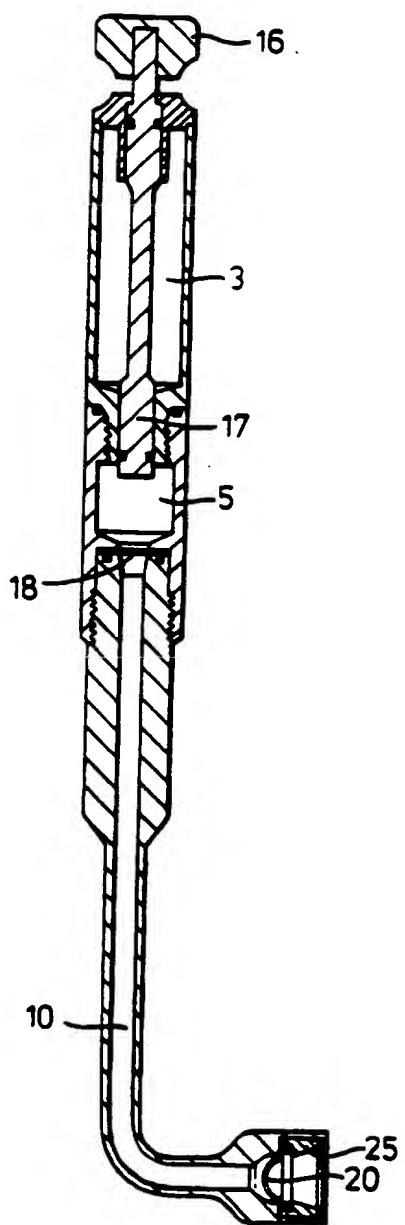


Fig.1.

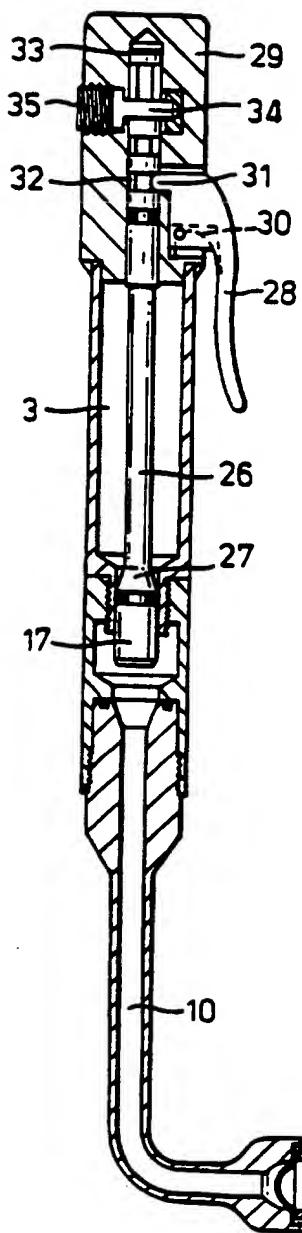
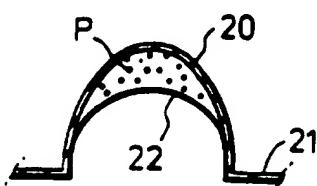
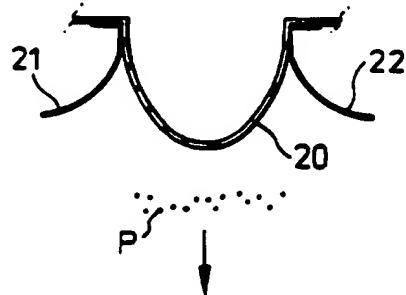


2/3

Fig.3.



3/3

Fig.4.**Fig.5.****Fig.6.**

INTERNATIONAL SEARCH REPORT

Intern. Application No.
PCT/GB 96/00340

A. CLASSIFICATION OF SUBJECT MATTER

A 61 M 5/307

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO, A, 94/24 263 (OXFORD BIOSC.) 27 October 1994 (27.10.94), the whole document, especially page 4, lines 22-34; page 5, line 11 - page 6, line 9; page 6, lines 20-25; page 7, lines 13-18; page 8, lines 17-26 (cited in the application). ---	1-4, 7, 8, 13-17, 19, 22- 31, 34
Y	US, A, 5 049 125 (CL. ACCARIES et al.) 17 September 1991 (17.09.91), fig. 5, abstract; column 1, lines 7-20; column 12, lines 37-56. ---	1-4, 7, 8, 13-17, 19, 22- 31, 34

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

'&' document member of the same patent family

Date of the actual completion of the international search

10 May 1996

Date of mailing of the international search report

04.06.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentstaan 2
NL-2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Telex 31 651 epo nl.
Fax (+ 31-70) 340-3016

Authorized officer

LUDWIG e.h.

INTERNATIONAL SEARCH REPORT

-2-

Internat'l Application No

PCT/GB 96/00340

C(Concise) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB, A. 686 344 (BELTON DICK.) 21 January 1953 (21.01.53), the whole document. ----	1, 19, 27, 28, 31

ANHANG

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX

to the International Search Report to the International Patent Application No.

ANNEXE

au rapport de recherche international relatif à la demande de brevet international n°

PCT/GB 96/00340 SAE 125666

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unter-richtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visé ci-dessus. Les renseigne-ments fournis sont donnés à titre indica-tif et n'engagent pas la responsabilité de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patient document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(e) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9424263	27-10-94	AU A1 64351/94 BR A 94064 CA AA 21594 EP A1 69311 FI A 954788 FR A0 954788 GB A0 9528069 HU A0 95020911 NO A 953994 NO A0 953994 NL A1 711003 GB A0 9321356 GB A0 9318407 GB A0 9307459 ZA A 9402442	08-11-94 02-01-96 27-10-94 24-01-96 06-10-96 06-10-96 06-03-94 28-12-95 06-10-96 06-10-96 06-01-96 08-12-95 20-10-96 02-06-96 10-04-96
US A 5049125	17-09-91	AT E 73479 AU A1 17934/88 CA A1 1519164 CO CO 10060214 DE DE 304272 DK DK 94272 EP A1 94272 EP A1 15691 EP B1 294272 ES T1 2030878 FR A1 2619706 FR B1 2629706 JP T1 1503397 JP B4 6033397 WO A2 0809189 WO A3 0809189 FR A1 51572 FR B1 2615739	15-04-92 01-03-93 22-04-93 07-12-93 09-04-93 17-05-93 18-03-94 18-11-94 13-10-94 22-05-94 16-11-94 30-03-94 01-12-94 09-03-94 02-12-94 19-01-90
GB A 586344		keine - none - rien	